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Bioavailability of diclofenac potassium at low doses

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Aim
Diclofenac-K has been recently launched at low oral doses in different countries for over-the-counter use. However, given the considerable first-pass metabolism of diclofenac, the degree of absorption of diclofenac-K at low doses remained to be determined. The aim of this study was to determine the bioavailability of low-dose diclofenac-K.

Methods
A randomized, three-way, cross-over study was performed in 10 subjects. Each received diclofenac-K, 22.5 mg via short-term i.v. infusion and orally at single doses of 12.5 mg and 25 mg.

Results
Mean (± SD) times to maximal plasma concentration (t_{max}) of diclofenac were 0.48 ± 0.28 h (12.5 mg) and 0.93 ± 0.96 h (25 mg). The absolute bioavailability of diclofenac-K after oral administration did not differ significantly in the 12.5-mg and 25-mg dose group (63.1 ± 12.6% *vs.* 65.1 ± 19.4%, respectively). The 90% confidence intervals for the AUC_∞ and AUC_t ratios for the two oral regimes were 82.6, 103.4% (point estimate 92.4%) and 86.2, 112.9% (point estimate 98.6%), respectively. These values were within the acceptance criteria for bioequivalence (80–125%).

Conclusions
Our data indicate that diclofenac-K is rapidly and well absorbed at low dose, and are consistent with a rapid onset of action of the drug.

Abbreviations
AUC, area under plasma concentraton-time curve; C_{max}, peak plasma concentration; CI, confidence interval; COX, cyclooxygenase; D, dose; *F*, absolute bioavailability; t_{max}, time to reach C_{max}.

Introduction

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that shows preferential inhibition of the cyclooxygenase-2 (COX-2) enzyme [1]. The normal formulations of diclofenac (monolythic acid-resistent coated dragée or tablet) may result in retention of the drug in the stomach for hours or even days, which may cause retarded absorption and delayed plasma peak concentrations [2]. Moreover, diclofenac has been shown to undergo considerable first-pass metabolism, limiting its oral bioavailability (50–60%) [3, 4].

To provide rapid pain relief, diclofenac potassium

(diclofenac-K) was launched as an immediate-release tablet [5–7]. In contrast to delayed release preparations of the sodium salt, diclofenac-K is formulated to dissolve under the acid conditions of the stomach [8]. Recently, an immediate-release formulation containing 12.5 mg diclofenac-K has been developed for sale over-the-counter. A flexible dosing regimen is proposed, starting with an initial dose of two 12.5-mg tablets followed by 1–2 tablets every 4–6 h as needed, to a maximum daily dose of 75 mg for up to 3 days for fever and 5 days for pain relief [9]. Data from clinical trials and postmarketing experience suggest that the safety and efficacy profiles of low-dose diclofenac-K are similar to those of low-dose ibuprofen given as a single dose of 200 mg and a maximum daily dose of 1200 mg [10].

The systemic absorption of diclofenac has been shown to be directly proportional to the dose within the range 25–150 mg [11, 12]. However, the question of whether diclofenac-K has a reproducibly high bioavailability at doses as low as 12.5 mg remains to be determined. The hepatic extraction of drugs exhibiting high first-pass metabolism may increase after lowering the dose, e.g. propranolol [13, 14]. These considerations prompted us to investigate the bioavailability and dose-proportionality of single oral doses of 12.5 mg and 25 mg diclofenac-K.

Materials and methods

Subjects and study design

Ten subjects (six male, four female), aged 26–38 years (30.3 ± 3.9 years, mean ± SD) with a mean weight of 73.9 ± 12.7 kg, participated in the study. The protocol was approved by the Ethics Commitee of the Universtity of Erlangen-Nürnberg. All subjects gave written informed consent prior to participation. All were healthy based on a medical history, physical examination, and routine laboratory screening. Exclusion criteria were a history of drug allergy, gastrointestinal disorders and cardiac, haematological, hepatic or renal diseases, pregnancy, concomitant medication on study days (including contraceptives) and repeated use of drugs that influence absorption and hepatic biotransformation during the 4 weeks prior to the study. In an open-label, three-way, crossover, three-period design subjects were randomly given 22.5 mg diclofenac-K administered as a 100-ml intravenous infusion over 15 min, and single oral doses of 12.5 mg and 25 mg (given as two 12.5 mg tablets) diclofenac-K (Voltaren® Dolo; Novartis Pharma, Basel, Switzerland). The tablets were administered with 100 ml water. The wash-out period between the treatments was 2 days. Drugs were administered at 08.00 h after an overnight fast with the last meal taken before 20.00 h. Intake of food was delayed for 3 h after drug administration. Peripheral venous blood samples were taken immediately before, at 15, 30, 45 min and at 1, 1.5, 2, 3 and 4 h after drug administration. For i.v. administration, additional blood samples were drawn at 2 and 7 min after the end of the infusion. Blood was collected into EDTA tubes, centrifuged, and plasma aliquots were stored at −80 °C for a maximum of 1 month.

Determination of diclofenac in human plasma

Reagents Diclofenac-K was kindly supplied by Irotec Laboratories Ltd. (Little Island, Co. Cork, Ireland). All other reagents were purchased from Merck (Darmstadt, Germany) and were of analytical grade. Acetonitrile was of high-performance liquid chromatography (HPLC) grade.

Sample preparation Samples were prepared by adding 1 ml phosphoric acid (1 μM) and 50 μl internal standard solution (10 μg niflumic acid ml^{-1} 0.03 M phosphate buffer) to 0.5 ml plasma. Subsequently, 5 ml dichloromethane was added and the samples were extracted for 15 min under constant shaking. After centrifugation, the organic layer was transferred into a glass tube and evaporated to dryness under nitrogen. The residue was dissolved in 250 μl mobile phase.

HPLC conditions Analytes were separated using a reversed-phase column (CC 125/4 Nucleosil 120-3 C8; Machery-Nagel, Düren, Germany) and a C8 precolumn insert. The column temperature was maintained at 24 °C. The mobile phase consisted of 22.5% (v/v) acetonitrile and 77.5% 0.03 M phosphate buffer (apparent pH 7.5). The flow rate was 1 ml min^{-1}. UV detection was at 282 nm. The lower limit of quantification of diclofenac was 25 μg l^{-1}. Validation of the method was performed according to Shah *et al*. [15]. The intra- and interday assay precision and accuracy for low (25 μg l^{-1}), medium (500 μg l^{-1}) and high (2500 μg l^{-1}) concentrations of diclofenac were 15% or less (high and medium concentration) and 20% (lower limit of quantification), respectively.

Data analysis

Plasma concentration-time curves were evaluated by noncompartmental analysis using WinNonlin® Version 3.3 (Pharsight, Mountain View, CA, USA). Maximal plasma concentrations (C_{max}) and times to C_{max} (t_{max}) were obtained directly from the raw data. The terminal half-life, $t_{1/2}$, was calculated as $\ln 2/\lambda_z$, where λ_z denotes the time constant of the terminal slope. The area under

the diclofenac plasma concentration-time curve from time zero to the last quantifiable plasma concentration (AUC_t) was calculated using the linear trapezoidal rule. The AUC from time zero to infinity (AUC_∞) was the sum of AUC_t and the extrapolated area under the concentration-time curve (equal to the predicted plasma concentration at the time of the last quantifiable diclofenac plasma concentration divided by λ_z). The absolute bioavailability (F) of diclofenac-K was calculated as (AUC_∞ oral)/(AUC_∞ i.v.) × 100, where the numerator and denominator were normalized to the oral or i.v. dose.

Comparisons of pharmacokinetic data obtained in the two study arms with oral administration (t_{max}, $t_{1/2}$, F) were performed using Student's paired t-test. For bioequivalence testing purposes, the 12.5-mg tablet served as the test formulation and the 25-mg tablet as the reference formulation. A linear mixed model (WinNonlin® Version 3.3) was used to calculate point estimates and their 90% confidence intervals (CI) on the basis of the dose-normalized and logarithmically transformed AUC and C_{max} values. The model considered subject (random effect) and formulation (treatment) as factors.

Results

The mean plasma concentration-time profiles of diclofenac after i.v. and oral administration are shown in Figure 1. The mean pharmacokinetic parameters are presented in Table 1. After oral administration of 12.5 and 25 mg diclofenac-K, plasma peak concentrations occurred at 0.48 and 0.93 h, respectively. The higher t_{max} in the 25-mg group was caused by a second concentration peak in three subjects (Figure 1C). However, differences in t_{max} values were not statistically significant. The terminal half-lives were similar in the three groups and the differences were not significant (Table 1).

The mean absolute bioavailability of diclofenac-K was 63.1% in the 12.5-mg and 65.1% in the 25-mg group (Table 1). The AUC_∞ after oral administration of 12.5 mg diclofenac-K was 50.4 ± 11.1% that of the 25-mg group. Furthermore, the C_{max}/AUC_∞ ratios were similar with the two oral formulations (12.5 mg, 1.12 ± 0.49 *vs.* 25 mg, 0.93 ± 0.26). To obtain additional verification of dose proportionality, bioequivalence of the oral diclofenac formulations was calculated. Point estimates and 90% CI were as follows: 92.4% (CI 82.6, 103.4) for the AUC_t ratio, 98.6% (CI 86.2, 112.9) for the AUC_∞ ratio, and 111.1% (CI 81.9, 150.6) for the C_{max} ratio. Thus, the 90% CIs of the ratios of the dose-normalized AUC values (12.5 *vs.* 25 mg) were within an acceptance

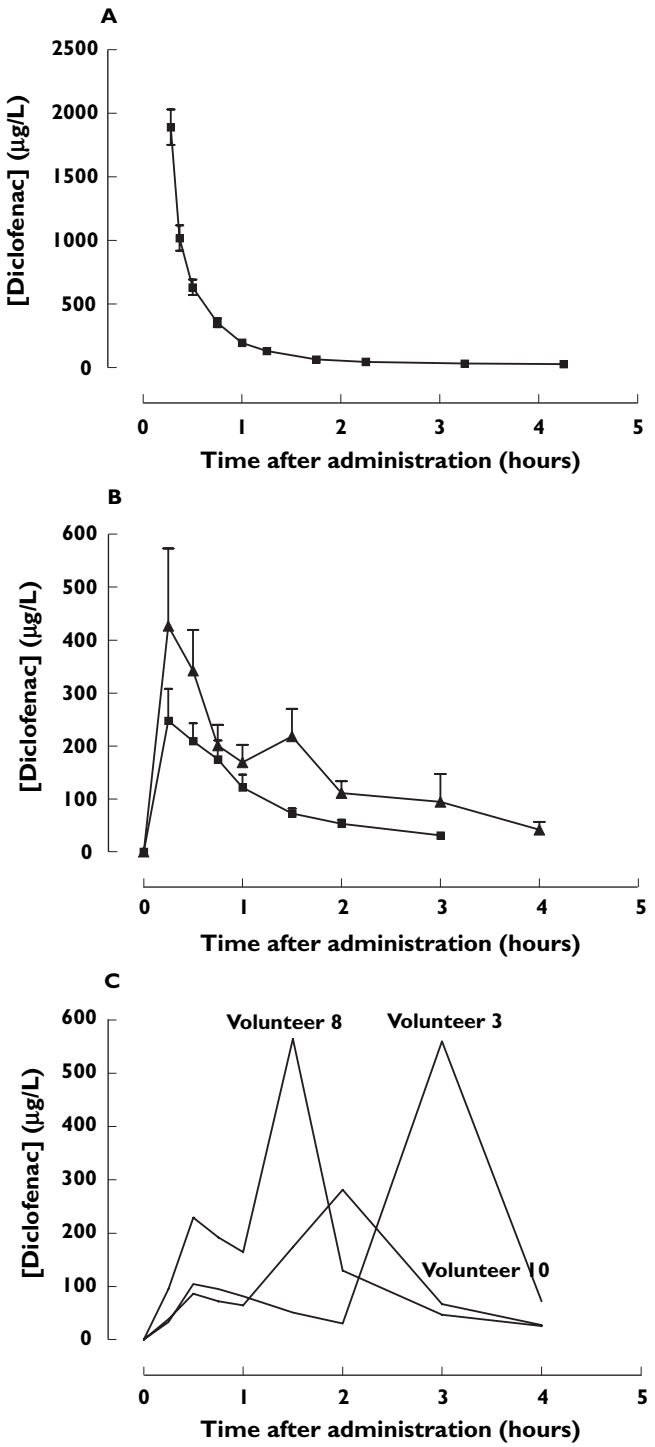

Figure 1

Mean diclofenac plasma concentration-time profiles (linear scale) following i.v. administration of 22.5 mg (■) diclofenac-K (A) and single oral administration of 12.5 (■) and 25 mg (▲) diclofenac-K (B). (C) The twin-peak pattern in three subjects who received 25 mg diclofenac-K. Values (A,B) are means (± SD) from 10 healthy subjects

Table 1
Mean pharmacokinetic parameters of diclofenac following the i.v. administration of 22.5 mg diclofenac-K or following single oral doses of 12.5 mg and 25 mg, and dose-adjusted pharmacokinetic parameters and absolute bioavailabilities following oral administration of diclofenac-K

	Diclofenac i.v. 22.5 mg			Diclofenac p.o. 12.5 mg			Diclofenac p.o. 25 mg		
Parameter	Mean (median)	SD	Range	Mean (median)	SD	Range or 90% CI*	Mean (median)	SD	Range or 90% CI*
C_{max} (μg l^{-1})	1892	439	1292–2506	334	162	89–577	588	313	248–1389
t_{max} (h)	0.28 (0.28)	0	0.28–0.28	0.48 (0.38)	0.28	0.25–1.0	0.93 (0.38)	0.96	0.25–3.0
AUC_t (μg l^{-1} h)	830	191	623–1127	270	78	126–381	580	165	320–913
AUC_∞ (μg l^{-1} h)	873	197	663–1174	304	79	136–418	613	166	346–924
$t_{1/2}$ (h)	0.9	0.3	0.4–1.6	0.8	0.3	0.4–1.3	0.8	0.2	0.6–1.0
C_{max}/D (μg l^{-1})				26.7	13.0	19.2, 34.2*	23.5	12.5	16.2, 30.8*
AUC_t/D (μg l^{-1} h)				21.6	6.2	18.0, 25.2*	23.2	6.6	19.4, 27.0*
AUC_∞/D (μg l^{-1} h)				24.3	6.3	20.6, 28.0*	24.5	6.6	20.7, 28.4*
F (%)				63.1	12.6	55.8, 70.4*	65.1	19.4	53.8, 76.3*

*C_{max}, Maximum observed plasma concentration; t_{max}, time to maximum observed concentration; AUC_t, area under the plasma concentration-time curve from time zero to the time of the last measurable concentration; AUC_∞, area under the plasma concentration-time curve from time zero to infinity; $t_{1/2}$, terminal half-life. D, dose; F, absolute bioavailability *Confidence interval.*

interval of 80–125%, whereas that of dose-adjusted C_{max} values was outside the upper limit.

All subjects completed the study 'per protocol', and all tolerated the medications well. One volunteer experienced vomiting of mild intensity 3 h after infusion of diclofenac-K, but recovered rapidly.

Discussion

The present study demonstrates that diclofenac-K is reproducibly and well absorbed after oral administration of a 12.5-mg dose. The data are consistent with previous investigations showing about a 50–60% oral bioavailability of diclofenac following single oral administration of 50 mg [3, 4]. Moreover, bioequivalence was confirmed by the 90% CI for the ratios of the dose-adjusted AUC values (12.5 mg *vs.* 25 mg) being within the acceptance range of 80–125%.

Diclofenac was detected in plasma within 15 min after oral administration of diclofenac-K, suggesting a rapid absorption of the salt. The higher t_{max} after administration of 25 mg diclofenac-K was mainly caused by secondary plasma peaks in three subjects. Possible mechanisms for secondary peaks include biphasic dissolution or gastric emptying, site-specific absorption, enterohepatic recycling or other physiological phenomena [16]. In the case of diclofenac, multiple peak phenomena have been often observed with immediate-release oral formulations due to pH-dependent solubility of the drug which changes within the gastrointestinal tract [7]. The occurrence of twin-peak patterns may also explain why the calculated bioequivalence interval for the dose-adjusted C_{max} values was outside the upper limit. In line with this observation, the European guidelines have previously acknowledged that this ratio is inherently more variable than the AUC ratio [17].

Our results are in line with recently published data showing rapid absorption of diclofenac-K-containing formulations [7]. In one study [6] an even faster rate of absorption was observed when diclofenac-K was given as sachets instead of tablets, suggesting that the former could be advantageous when a more rapid onset of analgesic effect is desirable.

Apart from its fast absorption and rapid onset of analgesia, the short half-life of diclofenac-K is of potential benefit compared with other nonprescription analgesics. Furthermore, of all over-the-counter analgesics, diclofenac shows the highest degree of COX-2 selectivity [1]. In contrast to ibuprofen, diclofenac does not antagonize inhibition of platelet aggregation by low-dose aspirin [18], which may be advantagous in patients taking the latter for cardiovascular protection.

In conclusion, our data indicate that there is no evidence of decreased bioavailability when diclofenac-K is given at a dose of 12.5 mg. Furthermore, diclofenac-K is rapidly absorbed at this dose, which is consistent with its rapid onset of analgesic action.

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